Research Article

Evaluating Multipulse Integration as a Neural-Health Correlate in Human Cochlear Implant Users: Effects of Stimulation Mode

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ABSTRACT

Previous psychophysical studies have shown that a steep detection-threshold-versus-stimulation-rate function (multipulse integration; MPI) is associated with laterally positioned electrodes producing a broad neural excitation pattern. These findings are consistent with steep MPI depending on either a certain width of neural excitation allowing a large population of neurons operating at a low point on their dynamic range to respond to an increase in stimulation rate or a certain slope of excitation pattern that allows recruitment of neurons at the excitation periphery. Results of the current study provide additional support for these mechanisms by demonstrating significantly flattened MPI functions in narrow bipolar than monopolar stimulation. The study further examined the relationship between the steepness of the psychometric functions for detection (d' versus log current level) and MPI. In contrast to findings in monopolar stimulation, current data measured in bipolar stimulation suggest that steepness of the psychometric functions explained a moderate amount of the across-site variance in MPI. Steepness of the psychometric functions, however, cannot explain why MPI flattened in bipolar stimulation, since slopes of the psychometric functions were comparable in the two stimulation modes. Lastly, our results show that across-site mean MPI measured in monopolar and bipolar stimulation correlated with speech recognition in opposite signs, with steeper monopolar MPI being associated with poorer performance but steeper bipolar MPI being associated with better performance.

If steeper MPI requires broad stimulation of the cochlea, the correlation between monopolar MPI and speech recognition can be interpreted as the detrimental effect of poor spectral resolution on speech recognition. Assuming bipolar stimulation produces narrow excitation, and MPI measured in bipolar stimulation reflects primarily responses of the on-site neurons, the correlation between bipolar MPI and speech recognition can be understood in light of the importance of neural survival for speech recognition.

Keywords: speech recognition, stimulation rate, detection thresholds, neural survival, electrode configuration

INTRODUCTION

In electrical hearing with cochlear implants, the slope of the function relating psychophysical detection threshold with stimulation rate in a fixed-duration pulse train is known as multipulse integration (MPI) (Kreft et al. 2004; McKay and McDermott 1998; Zhou et al. 2012). MPI has been shown to predict the sensory and neural conditions in implanted guinea pigs. Specifically, guinea pigs with higher spiral ganglion neuron (SGN) counts, higher spontaneous activity in the auditory nerve, and better hair cell survival were those that were better able to integrate electrical pulses, demonstrating a steeper decrease in detection threshold with increasing stimulation rate (Kang et al. 2010; Pfingst et al. 2011; Zhou et al. 2015). Slopes of the MPI functions reported in human subjects varied in a similar range as those observed

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in the guinea pig studies (Zhou et al. 2012). Such variability was observed across the stimulation sites along the electrode array, in a pattern that is specific to individual implanted ears. Whether the variation in MPI slopes observed in human subjects was related to the implanted ear's uneven neural survival pattern (Nadol 1997) or factors unique to human cochlear implant users, such as non-uniform electrode-neuron distance, has been explored previously in a series of psychophysical studies. The existing data in humans so far have shown that the MPI slopes are correlated with psychophysically estimated spatial selectivity of neural excitation. Steeper MPI was found to be associated with broader neural excitation demonstrated by a shallow-sloped forward-masking decay with masker-probe spatial separation or shallow-sloped psychophysical spatial tuning curves (Zhou and Dong 2017; Zhou and Pfungst 2016b). Using existing imaging data, Zhou and Pfungst (2016b) reported that the stimulation sites measured with steep MPI and broad forward-masking patterns were those that were estimated to have large electrode-neuron distances, typically located in the middle of the Nucleus 24RE array, rather than sites with substantial nerve loss.

Several mechanisms have been proposed to account for the dependence of MPI on a broad neural excitation pattern. The narrow interpulse interval in a high-rate pulse train reduces the probability that a single auditory fiber will respond to each pulse in the stimulus. Several factors contribute to this limitation, including neural refractoriness, accommodation to sub-threshold pulses, or adaptation from responding to dense stimulation (e.g., Boulet et al. 2016; Eggermont 1985; Javel and Shepherd 2000; McKay et al. 2013; Miller et al. 2011; Parkins 1989; Smith and Brachman 1982). Electrodes in a lateral wall position may produce a wider neural excitation than those close to the modiolus. The broad excitation allows a large neural population to operate at a low average firing probability (a low position on their dynamic range (DR)). The large neural population would be better able to respond to an increase in stimulation rate, compared to a small number of neurons already driven close to their maximum firing rate. The association between broad neural excitation observed at high stimulation rates and steep MPI (e.g., Zhou and Pfungst 2016b) might also reflect recruitment of neurons at the edge of neural excitation that were not responding at the low stimulation rates. Recruitment would depend on current spread and how the effect of rate on single-fiber behavior might be influenced by the average firing rate. Given the right condition, increasing stimulation rate will increase firing at the edge rather than the peak of excitation, producing a systematic broadening of the excitation pattern. Broad excitation may also increase the probability of

stimulating neurons that are inherently more temporally responsive, i.e., those with shorter refractoriness or less accommodation, due to their biophysical properties (Boulet et al. 2016). Evidence supporting this notion comes from studies that reported faster electrically evoked compound action potential (ECAP) recovery in monopolar stimulation (MP) compared to bipolar stimulation (BP) (Brown et al. 1996; Chatterjee and Kulkarni 2014), and an association between shorter time constants of psychophysical forward-masking recovery and steeper MPI (Zhou and Pfungst 2016a). A recent study however reported contradictory results that slower ECAP recovery was associated with a larger neural population (Botros and Psarros 2010). A logical extension of our previous findings that showed an association between steep MPI and broad neural excitation would be to compare MPI in MP and BP stimulation modes. Assuming that steep MPI requires an ideally sloped excitation pattern or excitation of certain width, we hypothesized that MPI functions would generally have shallower slopes in narrow BP stimulation than in MP stimulation due to either a narrower neural excitation provided by BP stimulation, or a steeper neural excitation pattern less ideal for recruitment. Further, assuming that the effect of current focusing is greater at larger electrode-neuron distances (Goldwyn et al. 2010), the effect of switching from MP to BP stimulation on MPI would be greater for stimulation sites that receive broader MP stimulation than those that receive relatively narrower MP stimulation.

Slopes of the MPI functions are highly correlated with those of the temporal integration functions (threshold-versus-duration functions) in both guinea pig and human cochlear implant subjects (Zhou et al. 2015). Previous studies have attributed the reduced temporal integration, in hearing impaired and cochlear implant listeners, relative to normal-hearing listeners, to the abnormally steep psychometric function for detection (Carlyon et al. 1990; Donaldson et al. 1997). If sensitivity to signal (d') increases more steeply with stimulus level, the level reduction needed to compensate for an increase in stimulus duration in order to maintain threshold (a given d') would be small (McKay et al. 2013). Steepness of the psychometric functions therefore may be an alternative explanation for differences in MPI, measured across different stimulation sites, subjects, or different stimulation modes. Zhou and Dong (2017) nonetheless reported that in MP stimulation, steepness of the psychometric functions for detection did not account for variance in MPI across stimulation sites or subjects. The second aim of the study was to extend the study by Zhou and Dong (2017) to examine the relationship between psychometric functions and MPI in BP stimulation.

The third aim of the study was to examine the relationship between speech recognition measured in MP stimulation and MPI across subjects. Factors that are important for speech recognition in the clinical default stimulation mode, i.e., MP stimulation, and may also influence MPI, are spread of excitation and neural health. That is, good neural survival or broad stimulation may both contribute to the required width or slope of the excitation pattern ideal for MPI. These two factors however may predict opposite correlations with speech recognition. Specifically, broad stimulation may lead to greater interactions between channels and poorer spectral resolution, and thus is disadvantageous for speech recognition especially for listening in noise (Jones et al. 2013; Won et al. 2007). On the other hand, good neural survival should support implant function and provide good speech recognition outcomes (Seyyedi et al. 2014). The relationship between MPI and speech recognition would depend on which of the two factors primarily drives the variation in MPI across sites and subjects, which may in turn depend on stimulation mode. If we assume that BP stimulation confines excitation to local areas and spatial spread becomes more even across sites and subjects compared to those in MP stimulation, neural survival would be a more heavily weighted factor driving the variance in MPI relative to spread of excitation. Steeper MPI measured in BP stimulation therefore may predict better speech recognition, since steeper MPI would indicate better neural survival. If MPI in MP stimulation is primarily affected by the variation in spread of excitation rather than neural survival, steeper MPI slopes in MP stimulation may predict worse speech recognition performance, because steeper MPI may be associated with channel interaction. The factors that are important for speech recognition may have different relative influences on MPI depending on the specific circumstances, and therefore, the relationship between MPI and speech recognition may also depend on those circumstances.

In summary, the aims of the present study were to (1) examine the effect of stimulation mode on MPI, (2) determine the relationship between psychometric functions for detection and MPI in BP stimulation, and (3) test the hypothesis that the relationship between MPI and speech recognition depends on stimulation mode.

METHODS

Subjects and Hardware

Nine ears, from seven subjects, implanted with the Cochlear Nucleus® devices were tested for the current study. The demographic features of the

subjects are shown in Table 1. Subjects used a laboratory-owned Freedom processor during all psychophysical testing. The psychophysical tests were administered using MATLAB programs that connected with the NIC II research interface. All subjects provided written informed consent to take part in the study. The use of human subjects was approved by the East Carolina University Institutional Review Board.

Experiment 1: Effect of Stimulation Mode on MPI

MPI was measured at two selected stimulation sites for each ear. The selected sites were either those that had published forward-masked spatial tuning curve data, or those chosen based on low-rate detection thresholds (80 pulses per second (pps)) that correlate with the sharpness of spatial tuning curves (higher thresholds were associated with broader tuning) (Zhou 2016; Zhou and Dong 2017). When using the 80-pps thresholds, two stimulation sites with relatively high and low thresholds were identified and evaluated for MPI. Only one site was tested for S3L due to time constraint. To measure MPI, psychophysical detection thresholds were obtained for two stimulation rates, i.e., 160 and 640 pps, in both MP (MP 1 + 2; two extracochlear ground electrodes) and BP (BP0; active and ground electrodes next to each other) stimulation modes. The stimuli were 300-ms biphasic pulse trains with a 75- μ s phase duration and an interphase gap of 8 μ s. The thresholds were first estimated using a method of adjustment, where the subjects adjusted the current level on their own to determine the level at which he/she could just detect the stimulus. The estimated thresholds were used to set the starting point of the adaptive procedure. In a three-alternative forced-choice paradigm, the signal was presented in one of the three intervals, chosen at random, and the subject was instructed to choose the interval that contained the signal. The signal started at a comfortable level and adapted based on the subject's response, following a two-down one-up rule. The signal levels at the last six reversal points out of a total of 12 reversals were averaged and taken as the threshold. MPI was quantified as the threshold decrease in dB per doubling of stimulation rate (dB/doubling) at two stimulation sites in two stimulation modes. The magnitude of the difference in MPI measured in MP and BP stimulation was then compared to the previously published tuning curve data (if available) measured at these sites.

Experiment 2: Relationship to Psychometric Function

Psychometric functions for detection, i.e., d' versus stimulus level, were measured for the 160-pps and 640-

Table 1

Subject demographics

Subject	Ear	Gender	Age (years)	CI use (years)	Duration of deafness (years)	Implant type	Etiology
S1	L	M	76.21	13.1	0.6	CI24R (CS)	Hereditary
S1	R	M	76.21	7.1	6.0	CI24RE (CA)	Hereditary
S2	R	F	49.41	2.9	41.5	CI24RE (CA)	Nerve damage
S3	L	F	65.29	9.2	3.35	CI24RE (CA)	Hereditary
S3	R	F	65.29	10.8	1.84	CI24RE (CA)	Hereditary
S4	L	F	56.22	3.8	0.4	CI24RE (CS)	Hereditary
S6	R	F	83.64	3.4	65.2	CI24RE (CS)	Hereditary
S7	R	F	69.83	4.6	27.9	CI24RE (CS)	Nerve damage
S10	R	F	65.10	2.4	12.4	CI24RE (CS)	Hereditary

pps stimuli in BP stimulation only, for subjects whose MP data had already been collected. New subjects who had not been previously measured for psychometric functions for detection in MP stimulation were tested in both modes. The functions were measured using the method of constant stimuli in a two-alternative forced-choice paradigm. The detailed method was published elsewhere (Zhou and Dong 2017). Briefly, sensitivity to a given signal (d') was tested for a range of current levels. The level range was estimated based on the adaptive threshold for that signal obtained for the MPI measure. The level range was estimated and modified to produce performance from chance (50 %) to 100 % correct. The step size of the level increment was typically five clinical level unit (CLU) (~ 0.78 dB) but was reduced if the level range was small. The number of levels tested for each function ranged from 4 to 8. Twenty trials were tested at a time, each containing a descending and an ascending run. The signal was presented at each current level for 120–240 times. The percent correct score as a function of stimulus level was transformed to a d' unit. The slope of each psychometric function was derived by performing a linear fit to log transformed d' unit against the current level in dB re 1 mA. Four psychometric function slopes (two rates $\times$ two sites), except for S3L, were calculated for each ear.

Experiment 3: Correlation with Speech Recognition

To investigate the relationship between MPI and speech recognition across ears, MPI was measured for the entire electrode array in both MP (MP 1 + 2) and BP (BP0) stimulation. The entire array was assessed assuming that all stimulated tonotopic regions contribute to speech recognition. MPI was again measured for two stimulation rates, i.e., 160 and 640 pps, using a method of adjustment. The test order of the stimulation sites and rates was fully randomized. The stimuli were 300-ms biphasic pulse trains with a 75- μ s phase duration and an interphase

gap of 8 μ s. During the test, the subject was instructed to use a large step size to bring the signal to a comfortably loud level and then bracket the level until a just detectable current level could be determined. The available step sizes for adjustment were 25 CLU, 5 CLU, and 1 CLU. In BP stimulation, S2R was not able to detect the 75- μ s/phase pulse train at the highest current level for the majority of the stimulation sites. Since a much longer phase duration would be required for the whole array, and that a longer phase duration may affect the shape of the MPI functions, S2R was removed from experiment 3 to ensure that correlation performed across subjects was not influenced by the change of stimulus parameter for one subject. For S4L, thresholds could not be recorded for stimulation sites 1–4 at 160 pps in BP stimulation. In data analyses for experiment 3, these sites were omitted for this subject.

Next, speech recognition was evaluated for listening in noise and in quiet using the subject's clinical everyday use map. For bilateral subjects, speech recognition was measured for one ear at a time. Volume adjustment was made, if the unilateral implant sounded too soft on its own. For speech recognition in noise, a speech reception threshold (SRT) for sentences was measured. CUNY (City University of New York) sentences were presented in a background of a white noise, amplitude modulated at 10 Hz with a 100 % modulation depth. The noise was presented alone for 1.5 s, during the sentence, and after the sentence for 0.5 s. The onset and offset of the noise were cosine ramped. The level of the amplitude-modulated noise was presented at 55 dB (A) SPL, and the level of the sentence was adapted using a one-down one-up rule in a step size of 2 dB. The subject was instructed to repeat the sentence she/he heard. The answer was counted as a correct response if the subject repeated the entire sentence correctly. Speech recognition in quiet was evaluated using TIMIT (Texas Instruments and Massachusetts Institute of Technology) sentences. The TIMIT sentences were spoken by 630 speakers of eight major

dialects of phonetically rich American English. Each sentence list contains 20 utterances. The sentences are grammatically correct utterances with minimal contextual cues. Choosing the relatively difficult speech material was to avoid ceiling effect that the subjects may have. The sentences were presented at a level of 65 dB (A) SPL. Each subject was instructed to repeat the heard sentence and the number of correct words identified was recorded. The SRT and TIMIT tests were repeated twice using different sentence lists and sometimes multiple times if there was a low test-retest reliability in the first two runs.

Statistical Procedure

IBM SPSS Statistics 23 (IBM, Armonik, New York) was used for statistical analyses. Paired-samples t tests were used to compare psychophysical results in MP and BP stimulation. A univariate general linear model was used to examine whether the MPI slope difference between stimulation modes was correlated with the slope of the spatial tuning curves, with the slope of the spatial tuning curve as co-variate and subject as a random factor. Another univariate general linear model was used to examine whether MPI co-varied with the steepness of the psychometric functions, with the steepness of the psychometric function as co-variate and subject as a random factor. A z test was used to compare the strength of correlations performed in MP and BP stimulation modes. Levene's test was used to examine homogeneity of variance in the slopes of the psychometric functions measured in the two modes. One-sample t tests were performed to examine whether the across-site mean MPI difference between stimulation modes was significantly different from zero for each ear. Stepwise regression models were used to examine whether speech recognition could be explained by MPI slopes measured in the two stimulation modes.

RESULTS

To examine the effect of restricting current field on MPI, the slopes were measured in MP and BP stimulation. Figure 1 shows that the MPI functions were steeper in MP than in BP stimulation, and the mean difference was statistically significant [$t(16) = 4.43$, $p < 0.001$]. It can be seen from Fig. 1 that the effect of stimulation mode was greater at some stimulation sites than others. With data combined across stimulation sites and ears, Fig. 2 shows that the effect of stimulation mode, i.e., the magnitude of difference in MPI between MP and BP stimulation, was dependent on the slope of the forward-masked

Fig. 1. MPI functions measured at two selected sites per ear in MP stimulation against those in BP stimulation. Symbols represent ears

spatial tuning curve measured at the site in MP stimulation, previously published in Zhou and Dong (2017) [$r = -0.58$, $p = 0.03$]. Specifically, using BP stimulation had a larger effect on MPI for stimulation sites that showed broader tuning in MP stimulation. However, when separating the two different sources of variance in the MPI slope differences using a univariate general linear model, i.e., between-site and between-ear variances, the correlations were no longer significant [between-site: $F(1, 6) = 1.87$, $p = 0.22$; between-ear: $F(1, 6) = 0.936$, $p = 0.531$].

The psychometric functions for detection measured in MP (red symbols) and BP (black symbols) stimulation are shown in Fig. 3. A portion of the MP

Fig. 2. Scatter plot of delta MPI slopes (data in BP stimulation minus MP stimulation) measured at selected sites per ear against the slope of the psychophysical forward-masked spatial tuning curves (previously published data in Zhou and Dong 2017). Symbols represent ears. The dashed line represents linear fit to the data combined across sites and ears

Fig. 3. Raw psychometric functions for detection. Data in each panel were collected from one ear. Red symbols represent data collected in MP stimulation. A portion of the MP data was published in Zhou and Dong (2017) and replotted here. Black symbols

represent data collected in BP stimulation. Symbols represent sites and stimulation rates. Site A was the site with relatively sharper tuning in a given ear, while site B was the site with relatively broader tuning

data has been published in Zhou and Dong (2017). Slopes of the psychometric functions for the 160-pps stimulus were significantly steeper than those for the 640-pps stimulus measured in MP stimulation [$t(16) = 3.32, p = 0.004$]. Considering the BP data, slopes of the psychometric functions for the 160-pps stimulus were also significantly steeper than those for the 640-pps stimulus [$t(16) = 4.18, p < 0.001$]. Comparing data between stimulation modes, slopes of the psychometric functions were comparable between stimulation modes for both the 160-pps stimulus [$t(17) = -0.17, p = 0.10$] and the 640-pps stimulus [$t(17) = -0.95, p = 0.35$]. Levene's test of homogeneity of variance indicated that slopes of the psychometric functions measured in BP stimulation were not significantly more variable than those measured in MP stimulation either [$F(1, 66) = 0.327, p = 0.57$]. Although the psychometric functions were comparable in their steepness and variability between stimulation modes, their relationship to MPI were different in MP and BP stimulation. Scatter plots of MPI slopes against psychometric function slopes for the 160-pps stimulus, 640-pps stimulus, and the averaged slopes for the two stimuli are shown for BP stimulation in Fig. 4. With data combined across sites and ears, Pearson's correlations

show that steepness of the psychometric functions for the 160-pps stimulus [$r = 0.54, p = 0.025$] and the average of the two stimuli predicted the steepness of MPI [$r = 0.61, p = 0.009$]. The trend of the data was that steeper d' growth with current level predicted shallower MPI. Considering the between-site and between-ear variances in MPI separately, results from univariate general linear models indicated that the only statistically significant result was that the mean psychometric function slopes accounted for the between-site variance [$F(1, 7) = 6.12, p = 0.04$] in MPI. The correlation between the steepness of MPI and the psychometric functions for the average of the two stimuli was statistically stronger in BP than in MP stimulation [$z = 1.85, p = 0.03$].

To examine the relationship between MPI and speech recognition, MPI was measured for all available stimulation sites in MP and BP stimulation (Fig. 5). Considering the MPI slopes, the general trend was for shallower slopes when BP replaced MP stimulation. For all tested ears, one-sample t tests revealed that the across-site mean MPI difference between MP and BP stimulation was significantly different than zero, as indicated by the asterisks ($p < 0.001$) shown in each panel next to the t statistics. However, the variability in MPI across the stimulation

Fig. 4. Scatter plot of the MPI slopes in BP stimulation against the slopes of the psychometric functions for detection (PFD) for the 160-pps stimuli (top panel), the 640-pps stimuli (middle panel), and the average of the two stimuli (bottom panel). The dashed line represents linear fit to the data combined across sites and ears. Symbols represent ears

sites was comparable between the two stimulation modes [$t(7) = 0.52, p = 0.62$].

The across-site mean MPI slopes in MP and BP stimulation (referred to hereafter as MP MPI and BP MPI) were entered into two linear regression models with SRT for CUNY sentences in an amplitude-modulated noise, and TIMIT sentence recognition in quiet as the dependent variables, respectively. The marginal correlations between MP MPI, BP MPI, and SRT scores are shown in the top two panels of Fig. 6. Note that the signs of the correlations were the opposite of each other (Fig. 6). That is, better SRT was associated with shallower MPI in MP stimulation, but with steeper MPI in BP stimulation. When entered stepwise into a multivariate regression, MP MPI was a strong significant predictor for SRT ($p = 0.004$). Although BP MPI did not have a significant marginal relationship with SRT, it explained a significant amount of unique variance in SRT, when MP MPI

was accounted for ($p = 0.04$). Jointly, MPI slopes measured in the two stimulation modes explained 88 % of the variance in SRT measured across subjects [$F(2) = 18.455, p = 0.005$]. The multivariate regression is equivalent of taking the difference between the two predictor variables and regressing against the dependent variable, which is shown in the bottom panel of Fig. 6. The marginal correlations between the two predictor variables and TIMIT sentence recognition in quiet are shown in the top two panels of Fig. 7. Similarly, the relationship between MPI and performance demonstrated the opposite trends depending on stimulation mode. Entering the two variables stepwise into a multivariate regression analysis, MP MPI was the only significant predictor for TIMIT sentence recognition explaining 56 % of the variance in performance [$F(1) = 7.64, p < 0.05$]. MP MPI and BP MPI jointly explained 67 % of the variance in TIMIT sentence recognition (Fig. 7, bottom panel), although the unique amount of variance explained by BP MPI was not statistically significant ($p = 0.24$), which was consistent with its non-significant marginal correlation with TIMIT sentence recognition ($p = 0.28$).

DISCUSSION

The current study aimed to examine three effects: (1) the effects of stimulation mode on MPI, (2) the effects of the steepness of psychometric functions for detection on MPI in BP stimulation, and (3) the effects of stimulation mode on correlations between MPI and speech recognition. Results showed that MPI generally became shallower in BP stimulation compared to that in MP stimulation. Variance of MPI in BP stimulation was accounted for by how steeply d' grows with current level under certain conditions, a relationship that did not exist in MP stimulation. Steeper MPI in MP stimulation was associated with poorer speech recognition, while steeper MPI in BP stimulation was associated with the opposite, i.e., better speech recognition. Jointly, they explained a large proportion of variance in speech recognition performance across subjects in noise and in quiet.

Effects of Stimulation Mode on MPI (Exp. 1)

In animal models, MPI is dependent on the count of SGNs near the stimulation site (Kang et al. 2010; Zhou et al. 2015). The electrode array implanted in the guinea pig subjects fills much of the space in the scala tympani, which results in small and even electrode-neuron distances across the array. Therefore, steepness of the MPI functions in these animal studies

Fig. 5. Across-site variation in MPI slopes in MP (red circles) and BP (black squares) stimulation. The t statistics in each panel show whether the across-site mean difference of MPI slopes between MP and BP stimulation was significantly different from zero (two asterisks indicate $p < 0.001$)

reflects primarily the “on-site” responses. If the electrode was stimulating a healthy area, then a steep MPI slope would be expected, due to a large neural population operating at a low average firing probability (a low position on their DR). This allows the neurons to further increase their firing rate when stimulus increases in rate. The surviving SGNs in healthy animals also tend to suffer less from neural degeneration (Zhou et al. 1995) or have higher spontaneous activity in the presence of surviving hair cells (e.g., Kang et al. 2010). These factors that co-vary with neural survival might also contribute to integration in the animal models. For example, spontaneous activity in the nerve may result in a stochastic pattern in the neural responses that help represent the high-rate pulse trains.

In human subjects with cochlear implants, previous studies suggested that MPI slopes comparable in magnitude to those measured in healthy guinea pigs were only found at stimulation sites with laterally-positioned electrodes. This could mean that the width of neural excitation (size of excited neural population) necessary for steep MPI to occur may only have been achieved via distant stimulation in human subjects without residual hearing thus presumably no spontaneous activity in the nerve. The broad activation would lower the average firing probability of the excited neural population countering the effect of reduced excitability in single units due to refractoriness and adaptation at a high stimulation rate. The

lateral wall electrodes may also allow an excitation pattern that systematically broadens with stimulation rate, where the neurons at the periphery of excitation that were not responding to low-rate stimulation were recruited to respond as rate increased. This recruitment process is consistent with previous findings that steeper MPI was associated with shallower forward-masking patterns or tuning curves measured at high rates (Zhou and Dong 2017; Zhou and Pfingst 2016b), but the idea that excitation systematically broadens with increasing rate is yet to be proven. With broad excitation, it has also been argued that it is likely to sample and stimulate neurons that are inherently better at coding dense stimulation such as those of high rates (Brown et al. 1996; Chatterjee and Kulkarni 2014).

If we assume that narrow BP stimulation produces narrow excitation, or a slope of excitation pattern less ideal for recruitment (steeper), then integration would reduce. The view that excitation is narrower in BP than in MP stimulation has been previously challenged because BP stimulation requires higher current levels to achieve a certain loudness compared to MP stimulation (Bierer 2007; Chatterjee 1999; Long et al. 2014; Pfingst et al. 1995) and the possible current spread may counter the effect of current restriction on selectivity. A recent study demonstrated that focused stimulation, even though operating at high current levels, is still more spatially selective than MP stimulation (Srinivasan et al. 2013), but no such

Fig. 6. Relationship between speech reception threshold (SRT) and MPI in MP and BP stimulation, as well as delta MPI (BP minus MP). The dashed line represents linear fit to the data. The correlation coefficients and p values represent the strength of the marginal relationships between SRT and the MPI slopes. Symbols represent ears

evidence was found for BP stimulation. Despite the uncertainty that BP stimulation produces a narrower or steeper excitation pattern than MP stimulation, results of the present study showed that MPI measured using adaptive procedures at selected sites was indeed shallower in BP stimulation than in MP stimulation (Fig. 1). Averaged MPI measured using method of adjustment across the whole array (Fig. 5) was also shallower in BP than in MP stimulation for each tested ear.

It is also clear from both Figs. 1 and 5 that the effect of stimulation mode was greater for some stimulation sites than others. Using published spatial tuning data previously measured on some of these sites (Zhou and Dong 2017), we showed that there was a trend that the effect of BP stimulation on MPI was

Fig. 7. Relationship between sentence recognition in quiet (TIMIT sentences) and MPI in MP and BP stimulation, as well as delta MPI (BP minus MP). The dashed line represents linear fit to the data. The correlation coefficients and p values represent the strength of the marginal relationships between sentence recognition and the MPI slopes. Symbols represent ears

smaller for sites that had already received relatively narrow stimulation by the MP electrodes (Fig. 2). That is, if a site is narrowly stimulated perhaps by a modiolar electrode, restricting the current field on that site would not greatly affect the width of excitation as it would on a broadly stimulated site. This provided further evidence that the manipulation in electrode configuration would indeed result in alternation in the neural excitation patterns.

Effects of Psychometric Function Steepness on MPI (Exp. 2)

The reduced MPI in BP stimulation mode can certainly also be due to the BP electrodes producing a steeper neural excitation growth with current level. This is because with steep neural excitation growth,

the current level adjustment needed for an increase in rate to maintain a fixed amount of neural activity would be small, hence shallower MPI (McKay et al. 2013). If we assume that the growth of sensitivity (d') to the signal is related to what occurs on the physiological level, i.e., the growth of neural excitation, the psychometric functions in BP stimulation would have to be steeper than those in MP stimulation to explain the reduced MPI. Current data however did not support this hypothesis showing comparable psychometric function slopes in BP and MP stimulation for both the 160-pps and 640-pps stimuli (Fig. 3). BP electrodes giving rise to steeper neural excitation growth is unlikely also because previous studies have in fact shown that loudness growth becomes shallower with the narrowing of current field (Bierer and Nye 2014; Chatterjee et al. 2000; Chua et al. 2011). Therefore, it seems more plausible to attribute the reduced MPI in BP stimulation to a reduced width or steeper slope of excitation as discussed earlier.

Zhou and Dong (2017) reported that in MP stimulation, steepness of the psychometric functions for detection was similarly unable to account for the differences in MPI found across stimulation sites, but in BP stimulation, as indicated by current data, such a relationship emerged. The psychometric functions share some similar features in MP and BP stimulation, namely, their steepness at each tested rate, comparable variability in steepness across sites and ears, and a significant difference in steepness for detecting the 160-pps and 640-pps stimuli. In both stimulation modes, the functions were steeper for the 160-pps stimuli than for the 640-pps stimuli (Zhou and Dong 2017 and current data). Regardless of these similarities, their relationships with the MPI functions were different in different stimulation modes. Separating the between-site and between-ear variances in MPI, we showed that a moderate amount of between-site variance in MPI could be explained by steepness of the psychometric functions averaged for the 160-pps and 640-pps stimuli. The reason that this relationship depended on stimulation mode is unclear. It could be that BP stimulation, via restricting the current field, reduces the variation in spatial selectivity of neural excitation along the electrode array, compared to MP stimulation. Therefore, in BP stimulation, neural excitation growth becomes a more heavily weighted factor that influences MPI, relative to MP stimulation.

Relationship between MPI and Speech (Exp. 3)

MPI measured in MP and BP stimulation, jointly, accounted for a large amount of variance in speech recognition performance across subjects. The interesting aspect of the finding was that the correlation between MPI and speech recognition reversed in

direction, depending on the stimulation mode in which MPI was measured. Specifically, steeper MPI measured in MP stimulation was associated with poorer SRT and sentence recognition in quiet, but steeper MPI measured in BP stimulation was associated with better performance. Because steep MPI is associated with broad spatial spread of neural excitation at a stimulation rate (900 pps/electrode) that is the clinical default for mapping (Zhou and Dong 2017; Zhou and Pfingst 2016b), MP MPI averaged across the stimulation site should therefore indirectly reveal the degree to which channels potentially interact with each other in the clinical default speech processing strategy. Previous research has shown that spectral-ripple discrimination threshold, which correlates with measures of channel interaction (Jones et al. 2013), is a strong predictor for speech recognition (Holden et al. 2016; Won et al. 2007). Poorer estimated spectral resolution, and greater channel interaction, predict worse speech recognition. Our data therefore are in agreement with the notion that poor spatial selectivity of neural excitation is detrimental for cochlear implant outcomes. One might use the same logic and argue that speech recognition should then be better in focused stimulation such as BP, relative to MP. We however should note that neural excitation produced by BP electrodes can be very different from that produced by MP electrodes in modiolar positions. For example, BP electrodes often produce bimodal excitation peaks at the active and return electrodes. It is also quite possible that the narrow excitation produced by the MP modiolar electrodes are more advantageous for speech recognition compared to that produced by BP electrodes. The fact that deactivation of MP electrodes associated with broad excitation improves speech recognition (e.g., Zhou 2016) also supports our interpretation of the current data.

If we assume that BP electrodes stimulate areas local to the stimulation sites (e.g., Bierer 2007), variations in MPI in BP stimulation would then be driven by the differences in the “on-site” neural responses rather than differences in spread of neural excitation resulted from factors such as electrode position. The “on-site” responses would reveal neural status near the site, including the inherent characteristics of the excited neurons which determine their refractory and accommodation behavior, as well as their quantity and healthiness as discussed earlier. BP MPI averaged across the stimulation sites would then reveal the average neural status in that ear. One might argue that if MPI in BP stimulation assesses the more local conditions, it should demonstrate greater across-site variation compared to that in MP stimulation, as other loudness-related psychophysical measures typically do (Bierer 2007; Pfingst et al. 2004). The fact that

the MPI functions were equally variable in MP stimulation compared to that in BP stimulation might be due to a point discussed earlier that the possible greater differences in spatial selectivity of excitation across channels in MP stimulation relative to that in BP stimulation might have contributed to a greater variability in MP MPI than expected.

There had not been strong evidence from studies that compared the postmortem conditions in the human cochlea with the implant functional data collected prior to death to show that speech recognition outcomes depend on neural survival (e.g., Fayad et al. 1991; Nadol et al. 2001). This could be due to the fact that the condition of the nerve at the time the speech recognition was measured was different from the condition at the time the histological analysis was made. Controlling for these potential subject-related variables, a recent study by Seyyedi et al. (2014) showed that bilateral implant users' ear asymmetry in speech recognition was accounted for by the ear asymmetry in SGN survival. Our data provided indirect evidence to support that neural survival, assuming that it is what the MPI functions reveal in BP stimulation, does contribute to speech recognition particularly in noise. Compared to MPI in MP stimulation, the unique amount of variance in SRT accounted for by MPI in BP stimulation was smaller. We however should caution the argument that neural survival is a less important factor for speech recognition than channel independence, since a moderate part of the variance in BP MPI was explained by the steepness of psychometric functions, or psychophysically estimated neural excitation growth, which might not be directly related to neural survival. If the assumptions that we made were all true, then a large amount of variance in speech recognition with cochlear implants would be determined at the peripheral level and the small unexplained variance would be accounted for by the central processes. Further research is then warranted to explore ways to improve electrode placement and retard peripheral degeneration for an optimal outcome.

The current data that related steep MPI functions in MP stimulation to poor speech recognition contradicted the findings reported by Zhou and Pfungst (2014), which showed that in bilaterally implanted subjects, steep MPI functions in MP stimulation were associated with better speech recognition. Zhou and Pfungst (2014) reported that in bilaterally implanted subjects, the ear measured with overall steeper MPI was the ear with better SRT and the magnitude of ear differences in MPI also predicted the magnitude of ear differences in SRT. This discrepancy may again be understood in terms of the relative contributions of the two factors, i.e., spread of neural excitation and neural survival, to the MPI

measure of interest. Taking the ear differences in MPI might have removed the factor of spatial spread, if we assume that the spatial spread is in part due to far electrode-neuron distance and electrode placement is similar in the two ears due to similarities in cochlear geometry and implant type. Thus, ear differences in MPI should mainly reveal the differences in neural status between the two ears rather than spatial spread, and the ear with steeper MPI should have better speech recognition. If the subject (rather than ear) differences in MPI were mainly driven by differences in spread of neural excitation due to different implant types and electrode insertion patterns rather than neural survival, then MPI should predict speech recognition in the opposite direction.

The current data support the following conclusions: (1) the effect of stimulation rate on behavioral thresholds (MPI) in human subjects is dependent on the width or slope of neural excitation, which could be affected by electrode-neuron distance or electrode configuration; (2) MPI is affected by neural excitation growth, estimated by the steepness of psychometric functions for detection, but this relationship only exists in BP stimulation; and (3) a significant amount of variance in speech recognition across subjects can be explained by channel independence and neural survival in the implanted ear, estimated by MPI in MP and BP stimulation respectively.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest The authors declare that they have no conflict of interest.

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